

WE CLAIM:

1                   1.       A method for identifying a compound capable of interfering with  
2 binding of an MRE11 polypeptide or fragment thereof, the method comprising the steps  
3 of:

4                   (i) combining an MRE11 polypeptide or fragment thereof with a  
5 polypeptide selected from the group consisting of RAD50 and NBS1, and the compound,  
6 wherein the MRE11 polypeptide or fragment thereof has nuclease activity and is encoded  
7 by a nucleic acid that hybridizes under stringent conditions to a nucleic acid encoding a  
8 polypeptide having an amino acid sequence of SEQ ID NO:2; and

9                   (ii) determining the binding of the MRE11 polypeptide or fragment thereof  
10 to a polypeptide selected from the group consisting of RAD50 and NBS1.

1                   2.       The method of claim 1, wherein the MRE11 polypeptide or  
2 fragment thereof and the RAD50 or NSB1 polypeptide are combined first.

1                   3.       The method of claim 1, wherein the MRE11 polypeptide or  
2 fragment thereof and the RAD50 and NSB1 polypeptide are combined.

1                   4.       The method of claim 1, wherein the MRE11 polypeptide or  
2 fragment thereof and the RAD50 or NSB1 polypeptide are expressed in a cell.

1                   5.       The method of claim 4, wherein the cell is a yeast cell or a  
2 mammalian cell.

1                   6.       The method of claim 5, wherein the MRE11 polypeptide or  
2 fragment thereof is fused to a heterologous polypeptide.

1                   7.       The method of claim 1, wherein the binding of the MRE11  
2 polypeptide or fragment thereof to RAD50 or NSB1 is determined by measuring reporter  
3 gene expression.

1                   8.       A method for identifying a compound that modulates cellular  
2 proliferation or chemosensitivity, the method comprising the steps of:

3                   (i) contacting the compound with an MRE11 polypeptide, the polypeptide  
4 encoded by a nucleic acid that hybridizes under stringent conditions to a nucleic acid  
5 encoding a polypeptide having an amino acid sequence of SEQ ID NO:2; and

6 (ii) determining the functional effect of the compound upon the MRE11  
7 polypeptide.

1 9. The method of claim 8, wherein the functional effect is measured  
2 *in vitro*.

1 10. The method of claim 9, wherein the functional effect is a physical  
2 effect.

1 11. The method of claim 10, wherein the physical effect is determined  
2 by measuring substrate binding to the polypeptide.

1 12. The method of claim 9, wherein the functional effect is a chemical  
2 effect.

1 13. The method of claim 12, wherein the chemical effect is determined  
2 by measuring endonuclease or exonuclease activity of the MRE11 polypeptide.

1 14. The method of claim 8, wherein the polypeptide is expressed in a  
2 eukaryotic host cell.

1 15. The method of claim 14, wherein the functional effect is a physical  
2 effect.

1 16. The method of claim 15, wherein the physical effect is determined  
2 by measuring ligand binding to the polypeptide.

1 17. The method of claim 14, wherein the functional effect is a chemical  
2 or phenotypic effect.

1 18. The method of claim 17, wherein the chemical or phenotypic effect  
2 is determined by measuring endonuclease or exonuclease activity of the MRE11  
3 polypeptide.

1 19. The method of claim 17, wherein the chemical or phenotypic effect  
2 is determined by measuring cellular proliferation.

1 20. The method of claim 19, wherein the cellular proliferation is  
2 measured by assaying for DNA synthesis or fluorescent marker dilution.

- 1                    21.    The method of claim 20, wherein DNA synthesis is measured by  
2    <sup>3</sup>H thymidine incorporation, BrdU incorporation, or Hoescht staining.
- 1                    22.    The method of claim 20, wherein the fluorescent marker is selected  
2    from the group consisting of a cell tracker dye or green fluorescent protein.
- 1                    23.    The method of claim 8, wherein modulation is inhibition of cellular  
2    proliferation.
- 1                    24.    The method of claim 8, wherein modulation is inhibition of cancer  
2    cell proliferation.
- 1                    25.    The method of claim 8, wherein modulation is activating sensitivity  
2    to chemotherapeutic reagents.
- 1                    26.    The method of claim 8, wherein modulation is activating sensitivity  
2    of cancer cells to chemotherapeutic reagents.
- 1                    27.    The method of claim 14, wherein the host cell is a cancer cell.
- 1                    28.    The method of claim 27, wherein the cancer cell is a breast,  
2    prostate, colon, or lung cancer cell.
- 1                    29.    The method of claim 27, wherein the cancer cell is a transformed  
2    cell line.
- 1                    30.    The method of claim 29, wherein the transformed cell line is PC3,  
2    HI299, MDA-MB-231, MCF7, A549, or HeLa.
- 1                    31.    The method of claim 27, wherein the cancer cell is p53 null or  
2    mutant.
- 1                    32.    The method of claim 27, wherein the cancer cell is p53 wild-type.
- 1                    33.    The method of claim 27, wherein the cancer cell is treated with  
2    bleomycin or etoposide.
- 1                    34.    The method of claim 8, wherein the polypeptide is recombinant.

1                    36.    The method of claim 8, wherein the compound is an antibody.

1                    37 .     The method of claim 8, wherein the compound is an antisense  
2     molecule.

1                    38 .     The method of claim 8, wherein the compound is a small organic  
2     molecule.

1                    39.    The method of claim 8, wherein the compound is a peptide.

1                    40.    The method of claim 39, wherein the peptide is circular.

41. A method for identifying a compound that modulates cellular proliferation or chemosensitivity, the method comprising the steps of:

(i) contacting the compound with an MRE11 polypeptide or a fragment thereof, the MRE11 polypeptide or fragment thereof encoded by a nucleic acid that hybridizes under stringent conditions to a nucleic acid encoded by a polypeptide comprising an amino acid sequence of SEQ ID NO:2;

(ii) determining the physical effect of the compound upon the SAK polypeptide; and

(iii) determining the chemical or phenotypic effect of the compound upon a cell comprising an MRE11 polypeptide or fragment thereof, thereby identifying a compound that modulates cellular proliferation or chemosensitivity.

42. A method of modulating cellular proliferation in a subject, the method comprising the step of administering to the subject a therapeutically effective amount of a compound identified using the method of claim 8.

43. The method of claim 42, wherein the subject is a human.

1                    44.    The method of claim 43, wherein the subject has cancer.

45. The method of claim 42, wherein the compound is an antibody.

- 1 46. The method of claim 42, wherein the compound is an antisense  
2 molecule.
- 1 47. The method of claim 42, wherein the compound is a small organic  
2 molecule.
- 1 48. The method of claim 42, wherein the compound is a peptide.
- 1 49. The method of claim 48, wherein the peptide is circular.
- 1 50. The method of claim 42, wherein the compound inhibits cancer cell  
2 proliferation.
- 1 51. A method of modulating cellular proliferation in a subject, the  
2 method comprising the step of administering to the subject a therapeutically effective  
3 amount of a MRE11 polypeptide, the polypeptide encoded by a nucleic acid that  
4 hybridizes under stringent conditions to a nucleic acid encoding a polypeptide having an  
5 amino acid sequence of SEQ ID NO:2.
- 1 52. A method of modulating cellular proliferation in a subject, the  
2 method comprising the step of administering to the subject a therapeutically effective  
3 amount of a nucleic acid encoding a MRE11 polypeptide, wherein the nucleic acid  
4 hybridizes under stringent conditions to a nucleic acid encoding a polypeptide having an  
5 amino acid sequence of SEQ ID NO:2.